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ORIGINAL PAPER

Bentonite clay: an efficient catalyst for the synthesis of 2-substituted benzimidazoles

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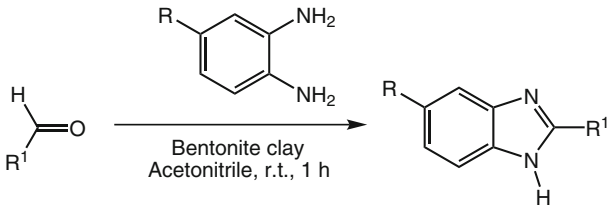
Abstract Benzimidazoles have been reported to have a wide range of biological and therapeutic properties. For this reason a variety of methods for their synthesis has been described, following one of the two general routes: the coupling of *o*-phenylenediamine and carboxylic acids or their derivatives using a strong acid and high temperature, or a two-step sequence that involves oxidative cyclodehydrogenation of Schiff's bases, obtained by the reaction of *o*-phenylenediamines and aromatic aldehydes. A simple, efficient, and environmentally friendly procedure for the synthesis of substituted 2- and 2,5(6)-substituted benzimidazoles is herein described. The procedure is carried out by treatment of *o*-phenylenediamine or 4-chloro-*o*-phenylenediamine with aryl or heteroaryl aldehydes. Bentonite clay is used as catalyst in dry acetonitrile at room temperature. This procedure has several important advantages, including short reaction times, large-scale preparations, easy isolation of the products, and good to excellent yields.

Graphical abstract



Keywords Bentonite clay · Benzimidazoles · Aryl aldehyde · Heteroaryl aldehyde · 4-Chloro-*o*-phenylenediamine · *o*-Phenylenediamine

Introduction

Benzimidazoles have received considerable attention due to their wide range of biological and therapeutic properties. For example, they have been investigated as anti-helminthic [1, 2], anti-parasitic [3, 4], anti-thrombosis, anti-inflammatory, anti-bronchoconstrictive, anti-neoplastic [5–8], neuroprotective [9], antifungal [10], and antiviral agents [11]. Therefore, it is not surprising that a wide variety of methods for synthesizing the benzimidazole nucleus have been developed and described in the literature.

Within the abundance of methods, there are two general routes for the synthesis of benzimidazoles. One is the coupling of *o*-phenylenediamine and carboxylic acids [12, 13] or their derivatives [10, 14–16] using a strong acid and high temperature (i.e., harsh experimental conditions). The other is a two-step sequence that involves oxidative cyclodehydrogenation of Schiff's bases, obtained by the reaction of *o*-phenylenediamines and aromatic aldehydes [17–19].

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A variety of catalysts, including $In(OTf)_3$ [20], functionalized silica gel with sulfonic acid [21], and $SiO_2/ZnCl_2$ [22], have recently been used for the synthesis of these compounds under strictly anhydrous reaction conditions.

In the search for more efficient and environmentally friendly methods, bentonite clay is herein considered as a catalyst. Given that bentonite clays work as both Lewis and Brönsted [23] acids, their acidic properties are well known. They are able to interact with carbon–oxygen double bonds to promote the addition of a nucleophile to the electrophilic carbon. Therefore, they are widely employed as heterogeneous catalysts in several interesting organic transformations, such as condensation reactions between carbonyl compounds and amines.

Thus, Eynde described the N–C bond formation catalyzed by bentonite clay in imidazolidine synthesis [24]. Likewise, Penieres reported the synthesis of benzimidazoles assisted by bentonite clay under IR irradiation [25]. Recently, Pitchumani reported the synthesis of 2-phenylbenzimidazole by two procedures. In one of them he used K10-clay as a heterogeneous catalyst, with water/methanol as solvent, and stirred the mixture for 24 h at room temperature. In the other he used Zn^{2+}-K10-clay under the same conditions. Yields were 26 and 98 % of the benzimidazoles [26].

An important focus of our group is the synthesis of molecules to be used as potential antimicrobial agents. Since we require an efficient and inexpensive method for benzimidazole synthesis, we decided to investigate bentonite clay as a possible catalyst in the absence of other Lewis acids (Table 1). We herein report a simple and straightforward procedure to obtain 2- and 2,5(6)-substituted benzimidazoles, starting with commercially available compounds and employing bentonite clay as a heterogeneous catalyst.

Results and discussion

The benzimidazoles **3a–3h** (Scheme 1) were prepared using *o*-phenylenediamine **2** and aryl (heteroaryl) aldehydes **1** in a 1:1.1 molar ratio, with bentonite clay (one part by weight relative to aldehyde) in dry acetonitrile. The reaction mixture was stirred at room temperature for 1 h.

Table 1 Benzimidazoles **3a–3h** prepared from *o*-phenylenediamines and (hetero)aryl aldehydes using bentonite clay (Scheme 1)

Prod.	R	R^1	Yield/%	M.p./°C	Lit. m.p./°C
3a	H	2-Thienyl	90	333–334	330–332 [19]
3b	H	2-Furanyl	75	289–290	284–286 [27]
3c	H	4-Nitrophenyl	89	328–329	308 [27]
3d	H	3-Nitrophenyl	94	213–215	204–206 [28, 29]
3e	Cl	2-Thienyl	64	228–229	226.5–227.5 [30]
3f	Cl	4-Nitrophenyl	64	224–226	257 [31]
3g	Cl	3-Nitrophenyl	64	245–246	243 [14]
3h	Cl	2-Nitrophenyl	64	110–111	108–109 [32]

Compounds **3a–3h** were obtained as beige amorphous solids in excellent yields, with melting points similar to those described in the literature. The products were characterized by analysis of their spectroscopic data. Their infrared spectra showed an intense absorption band near 3,300 cm^{-1}, which was assigned to the stretching frequency of the amino group of the imidazole ring. Additionally, compounds **3c**, **3d**, **3f**, **3g**, and **3h** showed an intense absorption band close to 1,500 cm^{-1}, which was assigned to the stretching frequency of the nitro group.

The proton nuclear magnetic resonance (^{1}H NMR) showed two kinds of signals for the substituted benzimidazoles. One is due to the benzimidazole nucleus and the other corresponds to the substituents. For such compounds substituted with a 2-thienyl or 2-furyl, the ^{1}H NMR spectra showed signals below 8 ppm with overlapping, thus making structural assignments for these benzimidazoles difficult. Nevertheless, the 2-nitrophenylbenzimidazole showed more separate signals, with some protons for the core observed below 8 ppm and other protons found above 8 ppm.

On the other hand, the carbon nuclear magnetic resonance (^{13}C NMR) for the synthesized compounds showed a different number of signals. Some of them were observed at around 129 ppm, which was assigned to the imine carbon (N=C–N) and ipso carbon (C–NO_2). In the case of the 2-furanyl substituent, there were signals at 144.5, 145.0, and 144.0 ppm, corresponding to the imine carbon (N=C–N), and the C-2′ and C-5′ furan system (C_2–O–C_5), respectively. The clorobenzimidazoles **3e–3h** showed a signal near 133 ppm, which was assigned to the ipso carbon (C–Cl).

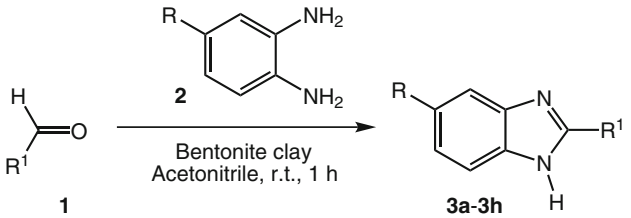
Conclusion

A new and a convenient one-pot synthesis of 2- and 2,5(6)-substituted benzimidazoles is reported, using bentonite clay as a heterogeneous catalyst. The synthetic strategy led to the formation of a benzimidazole pharmacophore that is well recognized for its diverse biological activity.

Experimental

Bentonite clay was donated by Dr. Delgado and was heated at 200 °C for 2 h. As bentonite clay swells when it absorbs water, it must be activated previous to use at 100 °C. Acetonitrile was dried with phosphoric pentoxide at room temperature. Melting points were determined on an

scheme 1



electrothermal melting point apparatus. Infrared spectra (IR) were recorded on a double beam Perkin-Elmer Model 1605 FT/IR spectrometer. NMR spectra were recorded in acetone-d_6 or DMSO-d_6 solution on a Gemini 200 or Eclipse 300 spectrometer, operating at 200 or 300 MHz for ^{1}H NMR and 50 or 75 MHz for ^{13}C NMR. Chemical shifts are reported in parts per million, relative to Me_4Si as the internal standard. Coupling constants J are expressed in Hz. Mass spectra were recorded on a double beam Joel JMS AX505HA spectrometer using the electron impact technique. All experiments were carried out at room temperature. Purification of the reaction mixtures was carried out by column chromatography using silica gel (Merck 70–230 mesh) as a solid support, or by recrystallization. The progress of the reaction was followed by thin layer chromatography (TLC) on plates of silica gel 60 F_{254}.

Typical procedure

A mixture of 434 mg *o*-phenylenediamine (4.02 mmol) and 500 mg thiophene-2-carboxaldehyde (4.46 mmol) was stirred for 45 min in the presence of commercial bentonite clay (500 mg) and 15 cm^3 dry acetonitrile. The reaction was monitored by TLC with ethyl acetate/*n*-hexane (2:3 v/v) as eluent. After completion of the reaction, solvents were removed under vacuum and the crude residue was purified by silica gel column chromatography (20 % ethyl acetate in *n*-hexane) or by recrystallization (ethyl acetate/*n*-hexane). The residual bentonite clay was washed with 30 cm^3 acetone, activated at 120 °C for 2 h, and directly reused in the following reactions with only modest loss of activity.

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